Summary of the
NIMH Research Roundtable Discussion on

Exploring Options to Assess Treatment Safety:
Community Assessment of the Safety of Psychotropic Medications in Children and Adolescents

Hosted by the National Institute of Mental Health on November 3, 2004, in Washington, DC.

Background: The use of psychotropic medications in children has increased dramatically in recent years. There is much concern in the community about possible effects of these drugs when given during development and potential long-term negative impacts. Standard clinical trials have an important but limited role in the assessment of drug safety because the duration of clinical trials is typically short and the sample size allows the detection of only frequently occurring adverse events. There is a need for information about long-term effects of treatments and on the possible association between treatment and infrequent but serious adverse events, such as suicidal behavior. For this reason, novel approaches to studying the safety of psychotropic medications in children are warranted.

Aims of the meeting:

- ☐ To identify opportunities to better use data from community naturalistic use of psychiatric medications among children and adolescents in order to inform about the safety of these treatments.
- ☐ To discuss strengths and limitations of such approaches as:
  - mining existing databases (e.g., Medicaid, HMOs);
  - improving existing databases by adding information in future data collection;
  - establishing new databases by conducting cross-sectional surveys of representative samples;
  - establishing prospective follow-up surveys of naturalistically treated community patients (e.g., registries of children treated for a particular condition and with a particular medication or combination of medications)

Main conclusions:

- The pediatric use of psychotropic medications has considerably increased over recent years. This substantial community utilization has the potential, if properly tapped, to broaden the information about the safety of psychotropic medications in children and thus complement the data derived from controlled clinical trials. Clinical trials are the best method to infer causal relationship between treatments and outcomes, but are limited by sample size, specificity of subjects, and short duration of treatment. There is a need to develop novel approaches to better use databases of naturalistically treated patients in the assessment of drug safety.

- Passive surveillance of marketed drugs (MedWatch) allows the detection of drug-related unexpected adverse events with low background incidence rate in the general population. The FDA Adverse Event Reporting System (AERS) database includes all spontaneous reports made by health providers and consumers since 1969 using a standard terminology (MedRA). Reporting rate for an adverse event can be calculated based on number of reports and estimated drug exposure in the population, and compared with the expected population rate. The system has major limitations, primarily due to its voluntary nature, including underreporting, duplicate reporting, and reporting biases (for instance, reporting is typically higher for the first 3 years of drug marketing). This method can only provide estimates of reporting rates (the ratio between number of reports of an adverse event and an estimate of drug exposure in the population), but not precise estimates of incidence rates. For adverse events that are expected as part of the condition being treated, such as suicidal behavior in depression, spontaneous reporting cannot be particularly informative.
- Active surveillance programs, where cohorts of patients being treated with a particular drug or class of drugs are systematically asked about possible adverse events, have been applied to specific drugs and situations (e.g., in utero exposure to medications), but, given their high cost, it appears unrealistic to mount such programs systematically for all marketed drugs potentially used by children. A more efficient option may be to improve existing medical databases.
- Clinical practice network databases, such as the General Practice Research Database in the U.K. (a network of general practitioners who routinely contribute data about the patients they treat), have been informative in the area of drug safety in several areas of medicine, including adult psychiatry. Their relevance in studying safety of psychotropics in children could be further explored.
- Pediatric and child psychiatry research networks can be of value for studying the clinical impact of more common adverse events on tolerability, adherence, and effectiveness of interventions in large, representative populations of patients (thus adding to the information from clinical trials that include more selected samples of patients).
- Health insurance databases have the potential to inform about drug safety. There are, however, wide discrepancies across databases in content, structure, and accessibility by researchers. Some private and public databases, such as that of Kaiser Permanente or those of some states' Medicaid, seem to be well poised to support surveillance and clinical epidemiology research. Some have ongoing collaborations with publicly funded Center for Research Education in Therapeutics, which can facilitate research activities. Health insurance databases could be used for retrospective surveys and also for prospective studies. Among the identified current limitations there is a dearth of outcome data relevant to safety, but these could be added. For example, a particular outcome that can inform about tolerability of treatment is the reason for not refilling a prescription. This information could be collected in electronic form at the pharmacy level. Approaches to adding drug safety information to existing databases that are feasible and inexpensive need to be identified.

Participant List

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Agenda

Wednesday, November 3, 2004
Metro Center Marriott Hotel, Washington, DC

8:30 am	Introduction Benedetto Vitiello, M.D. (NIMH)
8:45 am	Passive surveillance: its value and its limitations Andrew Mosholder, M.D., M.P.H. (FDA)
9:15 am	Mining national survey and Medicaid database: strengths and limitations Mark Olfson, M.D., M.P.H. (Columbia University)
9:45 am	The possible contribution of HMO databases Gregory Clarke, Ph.D. (Kaiser Foundation)
10:15 am	Break
10:30 am	The UK General Practice Research Database Hershel Jick, M.D. (Boston University)
11:00 am	The Child and Adolescent Psychiatric Trials Network (CAPTN) Mark Shapiro, M.A. and Susan Silva, Ph.D. (Duke Clinical Research Institute)
11:30 am	Pediatric Practice Research Networks Kelly Kelleher, M.D., M.P.H. (Ohio State University.)
12:00 n	General discussion
12:30 pm	Lunch break
1:30 pm	Discussion:

- How to take better advantage of existing databases?
- How to improve existing databases?
- Should new approaches (e.g., GPRD — like networks, registries focused on newly introduced drugs) be considered?
- Challenges and limitations in data interpretation.
- Practical obstacles to implementation.
- Possible solutions.

4:30 pm Conclusions

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Posted: June 2005